AMERICAN SOCIETY FOR MICROBIOLOGY

Public and Scientific Affairs Board

March 5, 2007

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Docket No. 2006D-0347

To Whom It May Concern:

The American Society for Microbiology (ASM) appreciates the opportunity to comment on "Guidance for Industry, Clinical Laboratories, and FDA Staff on In Vitro Diagnostic Multivariate Index Assays" published in the Federal Register on September 7, 2006 [Volume 71, Number 173, pp 52800-52801]. The ASM is the largest educational, professional, and scientific society dedicated to the advancement of the microbiological sciences and their application for the common good. The Society represents approximately 43,000 microbiologists, including scientists and science administrators in government, industry, and academic institutions working in a variety of areas, including biomedical, environmental, and clinical microbiology.

Reasons for ASM Support for an Oversight Program:

The ASM strongly supports the concept of oversight of high risk laboratory developed tests. Our concept of support is based upon our understanding of the requirements mandated by the Clinical Laboratory Improvement Amendments of 1988 (CLIA) for clinical and analytical validation of laboratory tests with an overall goal of assuring patient safety. The ASM recognizes that a primary goal of CLIA oversight of laboratory testing is the promulgation of sound laboratory practices. CLIA clearly states that Laboratory Directors are responsible for ensuring the safety and effectiveness of testing for the populations their laboratories serve. Meeting this responsibility can be difficult for laboratories because of challenges in gaining access to patient information and/or acquiring the specimens needed for verifying test performance. The ASM is appropriately concerned about the use of laboratory developed infectious disease diagnostic tests for which analytical and/or clinical validation may have been inadequate or incomplete.

ASM Concerns With the FDA Draft Guidance for IVDMIAs:

In its current form, the ASM finds the Food and Drug Administration's (FDA) Guidance Document on In Vitro Diagnostic Multivariate Index Assays (IVDMIAs) extremely

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difficult to understand and apply. We recognize that a laboratory developed IVDMIA would require FDA submission if it uses clinical data (from one or more IVD assays, and/or demographic data) to develop its algorithm. In addition, it must employ the algorithm to integrate the data points to calculate a patient result. And, it must provide a result that cannot be interpreted by clinicians without information from the developer regarding clinical performance and effectiveness. We also understand that FDA's oversight requirement will apply on a test by test basis, based upon its assessment of risk and complexity.

However, ASM has questions concerning the following: a) how would the concepts described in the preceding paragraph apply to infectious diseases diagnostics; b) what are the personnel and knowledge resources needed by the IVDMIA developing laboratory to submit a request for review and to respond to questions and issues raised by the FDA review process, c) what are the criteria to be used by the FDA to define and assess patient risk, d) how will the guidelines be applied to currently used tests, and e) how will the resources available at the FDA be augmented in order to complete the IVDMIA review process in a timely manner.

Initial Questions of Applicability of the Guidelines to Microbiologic Tests:

The ASM requests that any revision of the guidelines include examples of microbiologic tests; a few initial examples are provided below. We would also appreciate having the revised draft define the following for such tests: a) whether the test would require regulatory review, or not, and why it would or would not; b) what level of oversight might such a test require, and why, and c) what information would be required for FDA review.

Example 1:

An algorithm is applied to an antibiotic profile of a multiply resistant organism. Based upon the profile, the result predicts resistance of additional antibiotics that have not been tested, and that have no relatedness to those in the tested profile. The accuracy of the algorithm has been established by previous resistance testing of the unrelated antibiotics, and/or by clinical data on patient responses to the alternative drugs. The algorithm may have been validated in the laboratory offering the test, or in a laboratory other than the one in which the test is being used clinically.

Example 2:

A test reports probable resistance of a given patient's strain of HIV, HBV, or HCV. The determination is made by an algorithm that correlates genotypic properties or nucleic acid sequencing of the patient's virus with predicted resistance to specific antiviral agents. The correlation being used may reflect either qualitative or quantitative assessments of genomic structure. The predictive value of a given profile has been established by monitoring patient responses to the test drugs, patient response being defined in terms of the patient's CD_4 monitoring.

Example 3:

Molecular detection of resistance in *Mycobacterium tuberculosis* is used as a screening tool to quickly identify resistance, but results carry a disclaimer that the isolate may lack the predictive genotype and still be resistant by conventional testing.

Example 4:

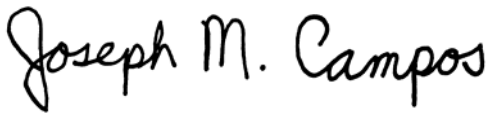
An algorithm combining cytology, HPV detection, and HPV genotype to determine whether a patient proceeds to colposcopy or receives follow up testing.

Example 5:

An algorithm in use for screening for HIV infection calls for pooling HIV antibody negative specimens and testing the pools for HIV RNA by RT-PCR. The idea is to identify recently infected patients who are not yet producing detectable antibodies (patients in the so-called window period).

The ASM supports the initiative of the FDA directed towards improving the efficacy and safety of laboratory developed tests. We appreciate the attention and care being applied to the development of effective strategies to achieve that goal, and we look forward to the further clarification and improvements to follow.

Sincerely,



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